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BF_3–OEt_2-mediated rearrangement of 4-substituted-5,5-diphenylazepan-4-ols

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Abstract—Synthesis of 2-(2-substituted-ethylidene)-3,3-diphenylpyrrolidines has been established starting from different 4-substituted-4-aryl-5,5-diphenylazepan-4-ols via boron trifluoride etherate-mediated rearrangement.

1. Introduction

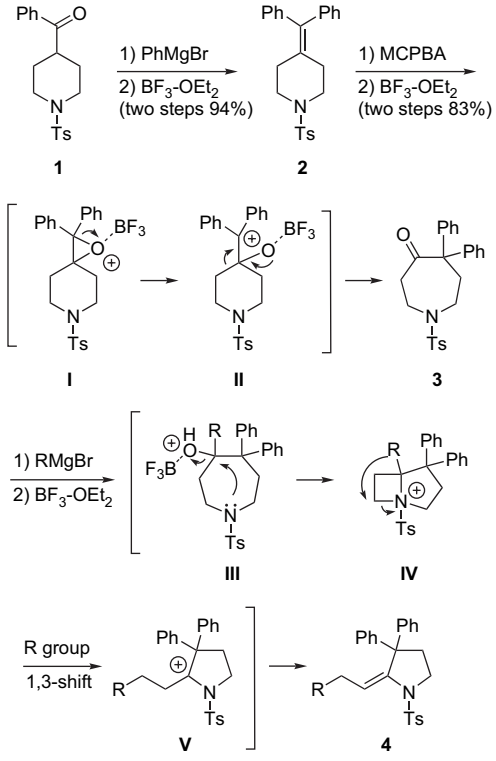
Recently, we explored some interesting rearrangement reactions toward different structural frameworks such as regioselective Baeyer–Villiger reaction, ring-contraction, and isomerization reaction via a convenient combination of *m*-chloroperoxybenzoic acid/boron trifluoride etherate.[1] Continuing our investigation on the application, treatment of 4,4-diphenylmethylenepiperidine with this combination and followed by treatment of the resulting compound with Grignard reagent/boron trifluoride etherate was further investigated.

Herein, a concise methodology for synthesizing the frameworks of seven-membered 5,5-diphenylazepan-4-one and five-membered 3,3-diphenylpyrrolidine is described from the starting material of 4-benzoyl-1-tosylpiperidine via (1) pinacol-type ring-expansion of six-membered 4,4-diphenylmethylenepiperidine with the combination of *m*-chloroperoxybenzoic acid and boron trifluoride etherate and (2) regiospecific ring-contraction of diphenylazepan-4-one with the combination of different Grignard reagents and boron trifluoride etherate in good yields.[2]

2. Results and discussion

For investigating the BF_3–OEt_2-mediated rearrangement, 4,4-diphenylmethylenepiperidine **2** was easily synthesized from 4-benzoyl-1-tosylpiperidine **1** via Grignard addition of compound **1** with phenylmagnesium bromide in tetrahydrofuran and followed by dehydration with boron trifluoride etherate in dichloromethane according to our preliminary experience.[3]

As shown in Scheme 1, 5,5-diphenylazepan-4-one **3** was obtained as a single isomer via pinacol-type ring-expansion



4a, Ar=CH_3, (80%); **4b**, Ar=C_6H_5, (82%);
4c, Ar=2-$CH_3C_6H_4$ (78%); **4d**, Ar=2-$CH_3OC_6H_4$ (70%);
4e, Ar=3-$CH_3OC_6H_4$ (72%); **4f**, Ar=2,6-$(CH_3)_2C_6H_3$ (80%)

Scheme 1. Synthesis of 2-substituted 3,3-diphenylpyrrolidines **4a–f**.

Keywords: *m*-Chloroperoxybenzoic acid; Boron trifluoride etherate; Grignard reagent; 5,5-Diphenylazepan-4-one; 3,3-Diphenylpyrrolidine.
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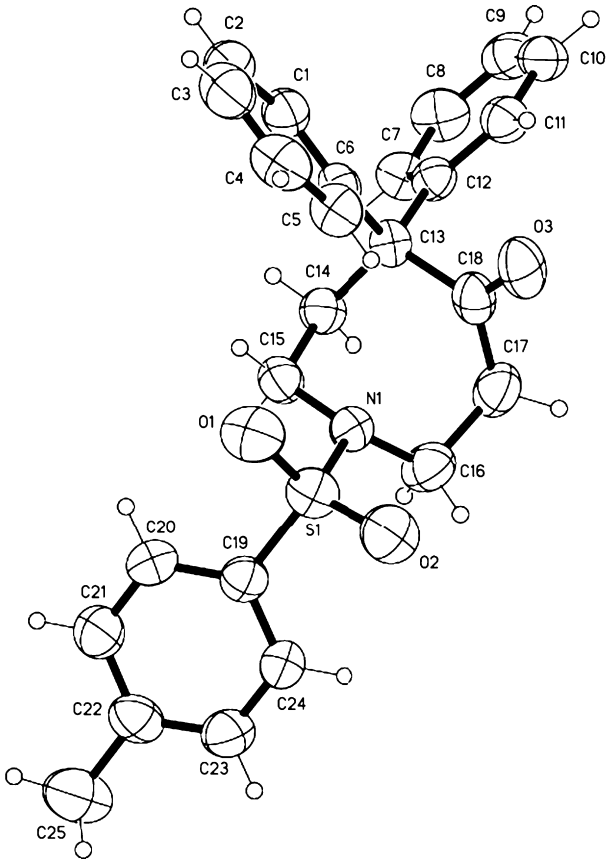

Diagram 1. X-ray crystallography of compound **3**.

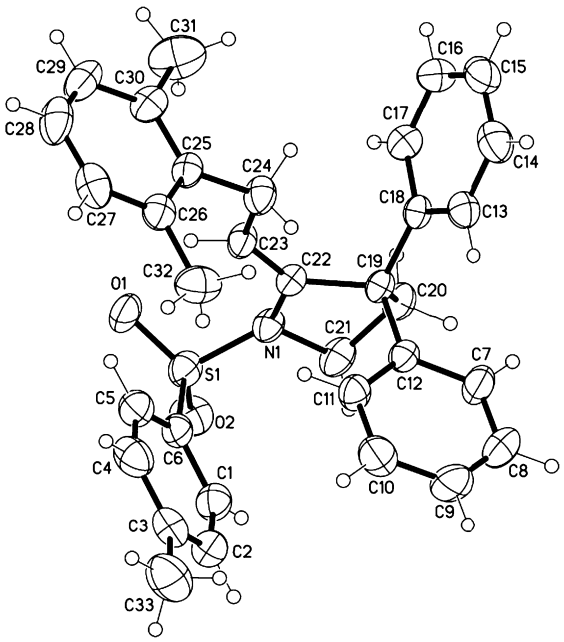

Diagram 2. X-ray crystallography of compound **4f**.

rearrangement of intermediates **I** and **II** with the combination of *m*-chloroperoxybenzoic acid and boron trifluoride etherate in 83% yield.[11] The characteristic structure of compound **3** was determined by single-crystal X-ray analysis as shown in Diagram 1.[4]

Next, on treatment of 5,5-diphenylazepan-4-one **3** with methylmagnesium bromide and followed by dehydration with boron trifluoride etherate in dichloromethane, the predicted product of 4-methyl-5,5-diphenyl-3-azepene with seven-membered skeleton was not afforded. Interestingly, the five-membered skeleton of 2-(2-arylethylidene)-3,3-diphenylpyrrolidine was generated in 80% yield during the rearranged procedure.[5] In order to demonstrate the regioselective ring-contraction reaction, compound **3** was treated with five arylmagnesium bromide reagents (**b**, C_6H_5; **c**, 2-$CH_3C_6H_4$; **d**, 2-$CH_3OC_6H_4$; **e**, 3-$CH_3OC_6H_4$; **f**, 2,6-$(CH_3)_2C_6H_3$) in tetrahydrofuran at −78 °C for 5 h and followed by boron trifluoride etherate-mediated rearrangement in dichloromethane at 0 °C for 15 min to afford 3,3-diphenylpyrrolidines **4a–f** as sole *E*-isomers in 70–82% overall yields. During the specific regioselective ring-contraction process, the other possible frameworks were not observed.

How is the ring-contraction of compound **3** initiated by boron trifluoride etherate? The explanation would be that boron trifluoride etherate-mediated dehydration of tertiary alcohol is controlled by involvement of the nitrogen lone pair on azepane skeleton (see Scheme 1). The initial event may be considered to be the formation of the intermediate **III**. Next, intermediate **IV** is formed by an intramolecular ring-closure of intermediate **III** and followed by the R group 1,3-shift of intermediate **IV**. Finally, compounds **4a–f** are yielded by proton abstraction of intermediate **V** under thermodynamic control. The unique structural skeleton of 3,3-diphenylpyrrolidine **4f** with 2-(2,6-dimethylphenyl)-ethylidene side chain was determined by single-crystal X-ray analysis as shown in Diagram 2.[4] It is worthy of note that geminal diphenyl group at the pyrrolidine ring could be useful building blocks in search of various compounds with different applications.[6]

3. Conclusion

In summary, we developed an easy and straightforward methodology for synthesizing two frameworks of seven-membered 5,5-diphenylazepan-4-one **3** and five-membered 3,3-diphenylpyrrolidine **4** via pinacol-type ring-expansion of six-membered 4,4-diphenylmethylenepiperidine **2** with the combination of *m*-chloroperoxybenzoic acid and boron trifluoride etherate and regiospecific ring-contraction of diphenylazepan-4-one **3** with the combination of different Grignard reagents and boron trifluoride etherate in good yields. Further novel application of this methodology with rearrangement and formation of new carbon–carbon bond is now underway.

4. Experimental section

4.1. General

Tetrahydrofuran (THF) was distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen

with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo.

4.2. 1-(4-Methylphenylsulfonyl)-5,5-diphenylazepan-4-one (3)

A solution of compound **2** (4.03 g, 10.0 mmol) in dichloromethane (100 mL) was added to a stirred solution of *m*-chloroperoxybenzoic acid (2.40 g, 75%, 10.4 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at rt for 2 h. The total procedure was monitored by TLC until the reaction was completed. Without further purification, boron trifluoride etherate (5 mL) was slowly added to a stirred solution of the resulting reaction mixture at 0 °C. The reaction mixture was stirred at rt for 15 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexane/ethyl acetate=4/1–2/1) afforded compound **3** (3.48 g, 83%). Mp 144–145 °C; IR ($CHCl_3$) 3019, 2918, 1708, 1594, 1493, 1339, 1168, 1090, 756, 699 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{25}H_{26}NO_3S$ 420.1633, found 420.1636; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J=8.5 Hz, 2H), 7.30–7.23 (m, 8H), 7.07–7.05 (m, 4H), 3.42–3.39 (m, 4H), 2.85–2.80 (m, 4H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.59, 143.74, 142.44 (2×), 134.84, 129.84 (2×), 128.50 (4×), 128.36 (4×), 127.23 (2×), 127.11 (2×), 64.39, 45.49, 44.67, 42.91, 36.91, 21.52. Anal. Calcd for $C_{25}H_{25}NO_3S$: C, 71.57; H, 6.01; N, 3.34. Found: C, 71.69; H, 6.26; N, 3.68. Single-crystal X-ray diagram: crystal of compound **3** was grown by slow diffusion of ethyl acetate into a solution of compound **3** in dichloromethane to yield colorless prism. The compound crystallizes in the orthorhombic crystal system. Space group $P2(1)2(1)2(1)$, a=9.6116(12) Å, b=10.1342(12) Å, c=22.210(3) Å, V=2163.4(5) $Å^3$, Z=4, d_{calcd}=1.288 Mg/m^3, absorption coefficient 0.176 mm^{-1}, $F(000)$=888, 2θ range (1.83–28.35°), R indices (all data) R_1=0.0613, wR_2=0.0889.

4.3. Representative procedure for compounds 4a–f

A solution of methylmagnesium bromide or different arylmagnesium bromide reagents (1.0 M in THF, 1 mL, 1.0 mmol) was added to a stirred solution of compound **3** (210 mg, 0.5 mmol) in tetrahydrofuran (20 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 5 h. The total procedure was monitored by TLC until the reaction was completed. Without further purification, boron trifluoride etherate (1 mL) was added to a stirred solution of the resulting reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. Water (5 mL) and ethyl acetate (20 mL) were added to the residue and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexane/ethyl acetate=4/1–2/1) afforded compounds **4a–f** in 70–82% overall yields.

4.3.1. 2-Propylidene-1-(4-methylphenylsulfonyl)-3,3-diphenylpyrrolidine (4a). Viscous gum; IR ($CHCl_3$) 3028, 2953, 1510, 1170, 1041 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{26}H_{28}NO_2S$ 418.1841, found 418.1844; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J=8.1 Hz, 2H), 7.21–7.06 (m, 8H), 6.90–6.87 (m, 4H), 5.94 (t, J=7.5 Hz, 1H), 3.55 (t, J=6.6 Hz, 2H), 2.59 (t, J=6.6 Hz, 2H), 2.47 (s, 3H), 1.31–1.20 (m, 2H), 0.66 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.96, 142.09 (2×), 141.81, 133.99, 129.38 (2×), 128.66 (4×), 128.31 (4×), 128.17 (2×), 126.69 (2×), 114.10, 60.07, 48.63, 41.22, 21.83, 21.25, 14.17. Anal. Calcd for $C_{26}H_{27}NO_2S$: C, 74.79; H, 6.52; N, 3.35. Found: C, 74.92; H, 6.83; N, 3.61.

4.3.2. 2-(2-Phenylethylidene)-1-(4-methylphenylsulfonyl)-3,3-diphenylpyrrolidine (4b). Viscous gum; IR ($CHCl_3$) 3025, 2917, 1731, 1494, 1163, 1031, 700 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{31}H_{30}NO_2S$ 480.1997, found 480.2001; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J=8.0 Hz, 2H), 7.23–7.03 (m, 11H), 6.96–6.94 (m, 4H), 6.85 (d, J=7.0 Hz, 2H), 6.16 (t, J=7.5 Hz, 1H), 3.57 (t, J=6.5 Hz, 2H), 2.64 (t, J=6.5 Hz, 2H), 2.52 (d, J=7.5 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.66, 142.22, 141.63 (2×), 140.79, 133.67, 129.15 (2×), 128.60 (4×), 128.34 (2×), 128.19 (4×), 128.13 (2×), 128.01 (2×), 126.67 (2×), 125.77, 111.02, 60.09, 48.37, 41.32, 33.37, 21.56. Anal. Calcd for $C_{31}H_{29}NO_2S$: C, 77.63; H, 6.09; N, 2.92. Found: C, 77.75; H, 6.32; N, 2.80.

4.3.3. 2-[2-(2-Methylphenyl)ethylidene]-1-(4-methylphenylsulfonyl)-3,3-diphenylpyrrolidine (4c). Mp 190–191 °C; IR ($CHCl_3$) 3019, 2950, 1656, 1598, 1493, 1341, 1161, 1030, 761, 665 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{32}H_{32}NO_2S$ 494.2154, found 494.2155; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J=8.0 Hz, 2H), 7.17–7.03 (m, 13H), 6.96 (d, J=7.5 Hz, 2H), 6.81 (dd, J=2.5, 6.0 Hz, 1H), 6.15 (t, J=7.5 Hz, 1H), 3.58 (t, J=6.5 Hz, 2H), 2.66 (t, J=6.5 Hz, 2H), 2.46 (s, 3H), 2.46 (d, J=7.5 Hz, 2H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.71, 142.46, 141.54 (2×), 138.87, 135.75, 133.91, 129.91, 129.21 (2×), 128.62 (4×), 128.26, 128.17 (4×), 127.99 (2×), 126.66 (2×), 125.87, 125.56, 109.64, 60.14, 48.33, 41.23, 30.47, 21.57, 19.21. Anal. Calcd for $C_{32}H_{31}NO_2S$: C, 77.86; H, 6.33; N, 2.84. Found: C, 77.69; H, 6.51; N, 2.94.

4.3.4. 2-[2-(2-Methoxyphenyl)ethylidene]-1-(4-methylphenylsulfonyl)-3,3-diphenylpyrrolidine (4d). Viscous oil; IR ($CHCl_3$) 3923, 2924, 1731, 1493, 1339, 1244, 1161, 1031, 755 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{32}H_{32}NO_3S$ 510.2103, found 510.2105; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J=8.5 Hz, 2H), 7.16–7.13 (m, 2H), 7.10–7.06 (m, 6H), 7.02 (d, J=8.5 Hz, 2H), 6.96–6.94 (m, 3H), 6.78 (t, J=7.5 Hz, 2H), 6.63 (dd, J=1.5, 7.5 Hz, 1H), 6.23 (t, J=7.5 Hz, 1H), 3.76 (s, 3H), 3.54 (t, J=6.5 Hz, 2H), 2.63 (t, J=6.5 Hz, 2H), 2.50 (d, J=7.5 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.17, 143.46, 141.93, 141.74 (2×), 133.69, 129.79, 129.06 (2×), 128.97, 128.72 (4×), 128.07 (4×), 128.05 (2×), 127.08, 126.51 (2×), 120.03, 110.67, 110.01, 59.97, 55.15, 48.29,

41.28, 28.10, 21.55. Anal. Calcd for $C_{32}H_{31}NO_3S$: C, 75.41; H, 6.13; N, 2.75. Found: C, 75.69; H, 6.41; N, 2.96.

4.3.5. 2-[2-(3-Methoxyphenyl)ethylidene]-1-(4-methylphenylsulfonyl)-3,3-diphenylpyrrolidine (4e). Viscous oil; IR ($CHCl_3$) 3025, 2957, 1654, 1598, 1489, 1340, 1161, 1032, 759 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{32}H_{32}NO_3S$ 510.2103, found 510.2106; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J=8.5 Hz, 2H), 7.18–7.05 (m, 9H), 6.97–6.95 (m, 4H), 6.72 (dd, J=2.0, 7.5 Hz, 1H), 6.49 (d, J=7.5 Hz, 1H), 6.39 (t, J=2.0 Hz, 1H), 6.13 (t, J=7.5 Hz, 1H), 3.78 (s, 3H), 3.56 (t, J=6.5 Hz, 2H), 2.64 (t, J=6.5 Hz, 2H), 2.48 (d, J=7.5 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.67, 142.46, 142.19, 141.62 (2×), 133.66, 129.19 (2×), 129.11, 128.62 (4×), 128.20 (4×), 128.04 (3×), 126.68 (2×), 120.77, 114.00, 111.26, 110.96, 60.10, 55.12, 48.35, 41.39, 33.46, 21.55.

4.3.6. 2-[2-(2,6-Dimethylphenyl)ethylidene]-1-(4-methylphenylsulfonyl)-3,3-diphenylpyrrolidine (4f). Mp 217–218 °C; IR ($CHCl_3$) 3019, 2952, 1636, 1339, 1161, 1028, 757 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{33}H_{34}NO_2S$ 508.2310, found 508.2312; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J=8.5 Hz, 2H), 7.22–7.13 (m, 8H), 7.05–6.92 (m, 7H), 5.73 (t, J=5.5 Hz, 1H), 3.57 (t, J=6.5 Hz, 2H), 2.67 (t, J=6.5 Hz, 2H), 2.52 (s, 3H), 2.17 (d, J=5.5 Hz, 2H), 2.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.90, 142.27, 141.21 (2×), 138.68, 135.97 (2×), 134.03, 129.30 (2×), 128.91 (4×), 128.20 (4×), 128.09 (2×), 127.91 (2×), 126.81 (2×), 125.80, 110.38, 60.61, 48.37, 41.73, 26.86, 21.62, 20.10 (2×). Anal. Calcd for $C_{33}H_{33}NO_2S$: C, 75.41; H, 6.13; N, 2.75. Found: C, 75.30; H, 6.32; N, 2.59. Single-crystal X-ray diagram: crystal of compound **4f** was grown by slow diffusion of ethyl acetate into a solution of compound **4f** in dichloromethane to yield colorless prism. The compound crystallizes in the monoclinic crystal system. Space group $P2(1)/n$, a=11.1735(18) Å, b=21.074(3) Å, c=11.7435(18) Å, V=2737.4(7) $Å^3$, Z=4, d_{calcd}=1.232 Mg/m^3, absorption coefficient 0.149 mm^{-1}, $F(000)$=1080, R indices (all data) R_1=0.0911, wR_2=0.1013, 2θ range (1.93–28.38°).

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4. CCDC 630263 (compound **3**) and CCDC 628562 (compound **4f**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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